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## Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2016

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Verberne, C. (2016). *Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

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Summary  
and Future Perspectives

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## SUMMARY

After curative surgery for colorectal cancer, patients are offered a control program. This is called colorectal cancer follow-up. The main goal of follow-up is early detection of recurrent disease.

Colorectal cancer follow-up is challenging for medical professionals in many ways. Improvements in preoperative staging, namely routinely using better imaging techniques, have led to a different pattern of recurrences. This affects follow-up methods. Patients expect that the doctor recognizes recurrent disease in an early phase; doctors have to know the right steps to take if any suspicion arises. With ameliorating surgical and ablative techniques for detected recurrences, more is possible; but on the other hand the population grows older and older so that certain options are barred. Medical research is based on rational comings and goings, however oncological care always comes with emotions.

So, research on colorectal cancer follow-up is also challenging. Since follow-up has many aspects, such as imaging and blood measurements, there is a risk of non-comparability between different studies with different follow-up methods; therefore a specific focus has to be made. This thesis has laid focus on the role of a long-known (and almost old-fashioned) aspect: the tumor marker Carcinoembryonic Antigen (CEA). This tumor marker rises in most patients (up to 80%) if recurrent disease is present and thus is a very valuable follow-up tool; however up to now, research has failed to define the best way to use CEA in follow-up in terms of frequency, threshold values, patterns of rise and its relationship to concurrent imaging. The research in this thesis helps to give more insight in the role of CEA in follow-up.

In Chapter 2, the hypothesis that CEA increase rather than absolute CEA value is important in the detection and curable options of recurrent disease is investigated. This hypothesis was posted several decades ago and based on the relation between tumor growth and height of CEA level, indicating a more important role for CEA rise rather than for absolute CEA value. However data to support the hypothesis were lacking. The review in Chapter 2 confirms that the hypothesis is still worthwhile; the diagnostic accuracy of serum CEA has been underestimated because of the incomplete methodology of clinical trials (regarding threshold value, measurement frequency and interpretation of CEA rise), but evidence supporting the clinical value of serum CEA rise for improving curative resection of recurrent disease is undisputedly available. Curative treatment options for recurrent disease have been improved considerably in the last decade. These findings were instantly tested with a phase-II trial. In this trial, the OptCEA trial, 241 patients operated for colorectal cancer were followed with frequent CEA measurements and assessment in case of a significant rise in CEA level; recurrences were detected in 28 patients (12%, mean follow-up time 18 months). Of 28 patients with recurrent disease, 12 patients (43%) were eligible for curative treatment. The sensitivity of the applied serum

CEA measurements was 79% and the specificity was 88% in a range between 2.5 and 10 ng/mL. The phase-II trial has led to the surmise that frequent CEA measurements and imaging based on CEA rise have high potential to detect recurrent disease early with less control visits. Furthermore it was found out that the logistics for frequent laboratory testing without concurrent doctor's visits were complex. To this end, a software program was developed to help doctors with large groups of patients in follow-up undergoing frequent laboratory measurements.

In Chapter 3, the testing of the software program is described. Patients' follow-up outcomes in terms of detection of recurrent disease and doctor's experiences with the software were compared between a group of patients followed with software-support with automated patient's letters and a group undergoing the usual follow-up care without software support. Results show that the software is safe for the patients' oncological care as well as convenient for medical specialists.

In Chapter 4, the role of CEA in patients treated for colorectal liver metastases (CRLM) is investigated. A large database containing all patients with treatable liver metastases between 1990 and 2010 in Groningen was retrospectively examined for the way in which the liver metastases were detected (by rising CEA, by positive routine imaging, or by both aspects at the same time). It turned out that up to 23% of patients had ongoing rise in CEA levels before liver metastases became apparent on routine scans. Receiver-Operating Curves (ROC) analyses were constructed to look for the most sensitive rise in CEA for the detection of liver metastases in as-if scenarios and a cost analysis showed high cost-effectiveness ratios for the use of CEA. It was concluded that CEA cannot be discarded as a follow-up tool in the search for liver metastases despite the ameliorating and more available imaging techniques.

Chapter 5 is considered the most important chapter of this thesis. In a prospective randomized-controlled trial, a new follow-up protocol was rolled out in eleven Dutch hospitals, aiming to detect recurrent disease earlier than the usual follow-up care (the current Dutch guideline). The study is called CEAwatch. The new protocol consisted of 2-monthly CEA measurements and imaging in the case of a significant CEA rise. This regimen was based on the results from the phase-II trial. 3,223 patients were included. After two years of prospective data collection, analyses showed that the intensified CEA-based protocol was associated with the earlier detection of recurrent disease and with a higher rate of curable options for the detected recurrences (35% vs 22%,  $P < 0.001$ ). Although 5-year survival have to be awaited, the results show that the new protocol is better in the detection of recurrent disease than the use of the Dutch guideline during the study period.

Chapter 6 investigates the dynamics of CEA in the applied new follow-up protocol (Chapter 5). The proposed schedule of 20% rise / two months confirmed by further rise four weeks later had a sensitivity of 55% and a specificity of 92% regarding the presence of RD and is suitable for use as a first-line screening in follow-up.

If clinical use of an intensive regimen has been approved because of demonstrated safety and efficacy, the balance between the additional effect and associated costs has to be assessed to make a rational decision with regard to broad implementation of the new regimen. In Chapter 7, the incremental cost-effectiveness ratios for recurrences are calculated. To detect one percent more recurrences in the intervention protocol compared to the control protocol, an additional amount of €94 is paid and in order to detect one percent additional curable recurrences, an extra amount of € 607 is spent for the intensified follow-up compared to standard follow-up. Considering the expected costs for palliative treatment (mostly chemotherapy) in case of non-curable recurrences, the associated costs are fairly acceptable. In Chapter 8 the psychological effects of the intensified follow-up are described. The intensified follow-up protocol posed no adverse effects on patients' attitude towards the follow-up and psychological functioning. In general, patients were more nervous and anxious at the start of the new follow-up protocol and had high expectations of it. As they spent more time in the follow-up and became more adapted to it, the nervousness and anxiety decreased and the preference for the frequent blood test became high.

Chapter 9 is a review of current literature on serum tumor markers for colorectal cancer follow-up other than CEA. Numerous markers have been proposed in the last decades. The review revealed three tumor markers other than CEA that have been shown to indicate recurrences in colorectal cancer: Tissue Polypeptide Antigen (TPA), Carbohydrate Antigen (CA)-242 and CA 72-4. Comparing of the studies turned out to be difficult. Therefore a prospective study of these markers is deemed necessary to investigate their real value, and to overcome design and inclusion biases. All stored blood samples have now been centered in one database and TPA measurements on these samples (with known CEA values, and known clinical patient's course) have been performed to investigate the combined value of TPA and CEA in colorectal cancer follow-up.

## FUTURE PERSPECTIVES

The evidence that more recurrences are treated with curative intent (Chapter 5) is not sufficient. A large recent British follow-up study, the FACS trial, compared three schedules of more intensive follow-up, namely regular CEA measurements alone, CT scanning alone, and CEA combined with CT scanning, with minimal follow-up. Significantly higher rates of curable recurrences were detected in the intensified follow-up schedules compared to minimum follow-up (respectively 6.7%, 8.0%, 6.6% and 2.3%). However the real clinical relevance of better follow-up strategies lies in survival gain and the most important next step on this topic is thus to study the effects of the new follow-up regimen on both disease-specific and overall survival. Results of studies performed in the past comparing different follow-up schedules show a consistent beneficial effect of schedules including

serum CEA measurements on survival. The FACS trial concluded that there was no survival improvement between the different follow-up protocols. Of course it has to be taken in mind that the randomisation process and the exact control schedules differed between CEAwatch and FACS, but FACS is the most recent study comparing different schedules and is comparable to the CEAwatch study. FACS investigators suggest that in earlier trials, patients might have suffered minimal recurrence disease at trial entry already; only when these recurrences grew larger they got detected, attributing to a survival benefit of intensive follow-up regimens. With the improved imaging investigative procedures at trial entry such as in FACS, this survival benefit would decrease or disappear. Given the low percentage of detected recurrences (7.5%) in our study, it might be possible that the CEAwatch study might lack the power to detect significant differences in survival between the two types of follow-up. And if these statistically differences are found, the discussion should be focused on the clinical relevance of the differences. The stepped-wedge design could also contribute to a lack of power of survival analyses. It is an elegant, but complex design and it has to be taken in mind that all patients are exposed to the intensified follow-up regimen later in time than to the control protocol. An Italian group has also investigated survival differences amongst different follow-up strategies in the GILDA trial. Furthermore the COLOFOL trial has been performed. This multinational prospective trial aims to compare a surveillance program including CEA, CT-scan of the liver and thoracic X-ray with a control protocol without any CEA measurements. Both GILDA and COLOFOL have finished patient inclusion and data collection, but the results on disease-free and overall survival from the trials are not yet published. After publication of these results, meta-analyses of the survival data from FACS, GILDA, COLOFOL and CEAwatch have to be performed; pooled data might lead to statistically significant differences, and more important, pooled data can help finding the clinically relevant influence of the used follow-up schedules on survival. At least, subgroup analyses on for example tumour stage and preoperative CEA levels can be performed and thus give insights in follow-up effects for subgroups. Broad implementation of the intensified, CEA-based follow-up cannot be performed without known effects on survival and the new 2014 Dutch guideline on colorectal cancer has therefore mentioned but not yet taken in the short-term effects of CEAwatch.

In the perspective of improving colorectal cancer survival, the role for the type and location of recurrences on the final outcome have to become clearer. Detailed investigation of the detected recurrences will be useful, since detected recurrences do not all have the same chances on curative treatment. The treatment possibilities and definite outcomes were debated and defined per recurrence, however the details of the exact way in which recurrences were detected and the given treatments per recurrence have to be further specified and investigated. Differences in approach per hospital can be studied, and both the curative treatments (surgical resection, ablative techniques for hepatic

metastases, stereotactic radiotherapy for pulmonary lesions, of which the definition of curability itself is questionable) and the palliative options (chemotherapeutic regimens, strictly supportive care, wait and see policy) have to be more specified.

A large part of the CEA serum samples has been stored. With the knowledge of other available promising tumor markers for colorectal cancer follow-up (Chapter 9), other laboratory measurements than CEA can be performed on these samples. All details and insights on CEA values could then be combined with other tumor markers or tumor marker panels. The first step, determining the Tissue Polypeptide Antigen (TPA) level in all stored samples, has already been taken. Other markers such as serum p53 antibodies and CA 19-9 could also be checked on both their independent value and their value additional to CEA. Maybe a tumor marker panel becomes standard of care.

In aiming for better patient's outcomes, more information can be hidden in the 18,000 CEA samples from the CEAwatch database. It opens up possibilities to find out more about the exact dynamics of CEA. In Chapter 6 the follow-up regimen has been studied on diagnostic accuracy, but with the current sensitivity of 55% for signalling recurrent disease, this is not optimal yet. The accuracy of different CEA rises and regimens can be modelled putting in all known CEA levels, tumour stage and patients' clinical course for those who had recurrent disease; in this way the pattern of CEA rise with the ideal combination of sensitivity and specificity can be defined at patient's or subgroup level. The relationship between patient's preoperative clinical performance and the value of serial CEA concentrations, as well as the role of tumour stage, can be further specified. Since not only patient's and tumour's characteristics are known but also all recurrences will be studied in detail, a model on the value of CEA in a specific patient group can lead to a flowchart of recurrence probability and the role that CEA can play in detecting that recurrence. The value and sensitivity of radiological imaging types (ultrasound, CT) must be further studied in the current database to implement imaging in the model as well. Data on the clinical course per patient continues to be collected for the whole study group and thus can be put into the model. In this way we can work in the direction of patient-tailored, optimized follow-up.

After modelling the optimal way of CEA-based follow-up based on patient and tumor characteristics, the way it is offered to the patients must be modernized. Using e-health, one could work with patient-personalized medical files. Per hospital, a medical professional such as a nurse practitioner can be in charge of all patients in follow-up. This person will be easily and frequently accessible for all patients, possibly improving patient's experiences with the hospital. This person has more time for patients than the medical specialist, a reason why he or she could also have time to help patient with coping of their disease.

The concept of a nurse practitioner is, of course, not new and has already been introduced in several hospitals, for example for breast cancer care. This role can most certainly be ameliorated. He or she can support follow-up more and better if modern



media in daily practice are put in. Patients now get their laboratory CEA results at the outpatient ward or by post mail or telephone. A mobile application (app) gathering the latest values can be developed; if follow-up is patient-tailored, this e-health app could feed forward a possible next step based on pre-defined algorithms per patient or patient's groups to the medical professional. At his/her turn this nurse practitioner can feed back the information to the patient through the app. Alternatively, patients only get information if CEA is elevated on a "no news is good news" base; it has to be investigated if this model would be appreciated by patients. The nurse practitioner can discuss elevated CEA measurements with the medical specialist after which imaging can be asked for directly (avoiding the step that the patient has to be seen first). Instead of choosing ultrasound of the liver or CT scan, the more sensitive alternative of the PET-CT can be requested since with elevated CEA, the presumption of recurrent disease in certain subgroups will be better predictable. Using the app, each patient is the owner of his medical data and he could be more involved in decision making, enlarging patient empowerment. In this way, an old and almost old-fashioned tumor marker can efficiently revive in current times.









*Augustus 2015*

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